REMARKS

Claims 2, 3, 6, 7, 9, 10, 12, 13, 15, 16, and 18-26 are active in this application.

The rejection of Claims 2, 3, 6, 7, 9, 10, 12, 13, 15, 16, and 18-26 under 35 U.S.C. §112, first paragraph ("written description"), is respectfully traversed.

The present invention provides, in part, an isolated coryneform bacterium wherein an argR gene on a chromosome of the bacterium is disrupted, and the argR gene has the nucleotide sequence shown in SEQ ID NO:17 or is obtained from chromosomal DNA of the bacterium by PCR under a condition with oligonucleotide primers having a nucleotide sequence shown in SEQ ID NO:15 and SEQ ID NO:16, wherein the condition is a condition in which annealing is performed at 58°C (see Claim 2).

The Office has alleged that the specification fails to provide an adequate number of representative species to support the genus provided in the present claims. Applicants respectfully disagree for the reasons below.

Applicants direct the Examiner's attention to MPEP § 2163.02:

> An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

The Office asserts "the specification does not provide a written description of any nucleotide sequence other than the nucleotide of SEQ ID NO: 17" (February 24, 2004 Office Action, page 3). The Examiner also dismisses the argument that the PCR methods, conditions, and protocols are known the art, as not being at issued. However, Applicants note that PCR amplification is directly relevant in the analysis of the description of the claimed invention. As

stated above, the claimed invention pertains, in part, to a DNA obtained from chromosomal DNA of the bacterium *by PCR* in which annealing is performed at 58°C with oligonucleotide primers having a nucleotide sequence shown in SEQ ID NO:15 and SEQ ID NO:16. Accordingly, Applicants note that PCR is a limitation in Claim 2 that cannot be summarily dismissed.

What the Examiner has apparently failed to appreciate is that SEQ ID NOs: 15 and 16 are 25 nucleotides long and contain a specific nucleotide sequence. Accordingly, their statistical occurrence in the genome would be on the order of 1 per 1 x 10^{15} bp[1], which greatly surpasses the typical size of a bacterial genome. As such, the amplification product from PCR with SEQ ID NOs: 15 and 16 is a *specific sequence* that would necessarily code for the argR gene.

Moreover, Applicants note that the argR genes are highly conserved among coryneform bacteria (page 14, lines 8-13). Further evidence of the sequence conservation of the argR gene is provided by the **enclosed** argR gene (accession number AF041436) sequence from *Corynebacterium glutamicum* (which is similar to *Brevibacterim flavum*, a coryneform bacteria, disclosed in the specification). The conservation of sequence is extremely important as the definition of the PCR primers and the annealing condition will dictate the stringency of hybridization and fidelity of the resultant priming event. As with a specific PCR protocol, a description of the specific primers and the PCR conditions would necessarily describe the genus of permissible amplification products.

Accordingly, the present invention is sufficiently described within the context of 35 U.S.C. §112, first paragraph. Applicants request withdrawal of this ground of rejection.

The rejection of Claims 2, 3, 6, 7, 9, 10, 12, 13, 15, 16, and 18-26 under 35 U.S.C. §112, first paragraph ("enablement"), is respectfully traversed.

For the reasons set forth above, Applicants submit that the skilled artisan would be able to practice the full scope of the claimed invention with nothing more that ordinary skill. Specifically, by having specific PCR primers and defined annealing conditions the skilled artisan would only amplify sequences that are an argR gene and, thus, within the scope of the claimed invention. However, it is the scope of the argR gene obtained by PCR that is at issue.

MPEP §2164.04 states:

> "A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

The claimed invention defines, in part, the argR gene as being "obtained from chromosomal DNA of the bacterium by PCR with oligonucleotide primers having a nucleotide sequence shown in SEQ ID NO:15 and SEQ ID NO:16." In this regard, Applicants note that the determination of PCR conditions would be readily appreciated by one of skill in the art with the present application in hand. Specifically, Applicants direct the Examiner's attention to Example 3 (pages 25-30), which clearly directs the artisan on how to make and use the present invention. As such, Applicants submit that one possessing much less than routine skill in the art can practice the present invention.

Applicants note that this ground of rejection is based on the Examiner's perception that the PCR product of SEQ ID NO: 15 and SEQ ID NO: 16 would embrace a large number of sequences of diverse sequence and structure. The Examiner further states that "any

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[1] $N = 4^{25} = 1.12 \times 10^{15}$

polynucleotide of any nucleotide sequence can be amplified and that undue experimentation must be performed to screen each and every PCR product." (February 24, 2004 Office Action, page 4) Applicants disagree with this assertion by the Examiner. In fact, this assertion by the Examiner lacks any scientific basis for the following reason.

Applicants again note that each of SEQ ID NOs: 15 and 16 are 25 nucleotides long and, as such, their statistical occurrence in the genome would be on the order of 1 per 1 x 10^{15} bp. In contrast bacterial genomes, such as coryneform bacteria only have about 1 x 10^{6} bp. Accordingly, even under low stringency conditions, which permit mismatches in the primer hybridization step, PCR would still be expected to produce the target gene. This is especially true when the high sequence homology of argR genes among coryneform bacteria is taken into account (page 14, lines 8-13). In fact, the high homology of argR gene would further simplify the screening and analysis to verify that the gene obtained by PCR is actually the argR gene (for example, by performing a restriction digest at a conserved restriction site that is within the argR gene sequence and is unique to the family of argR genes as compared to the cloning vector). Further evidence of the sequence conservation of the argR gene is provided by the **enclosed** argR gene (accession number AF041436) sequence from *Corynebacterium glutamicum* (which is similar to *Brevibacterim flavum*, a coryneform bacteria, disclosed in the specification).

Moreover, Applicants remind the Examiner that MPEP §2164.05(a) states:

> The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public... The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date.

PCR conditions including the temperature and buffer conditions required to ensure adequate stringency such as to reduce and/or eliminate faulty priming would be readily

appreciated to the artisan. As the Examiner surely can not contest, PCR methods, conditions, and protocols are well appreciated in the art and are so routine that this job is commonly assigned to a lab technician or undergraduate student and, thus, it is not the burden of the Applicants to detail each and every permutation of the technology that would result in the genes within the scope of the claimed invention. In fact, the Office encourages that Applicants not burden them with such well-known methods. Despite this Office mandate, Applicants note that Example 2 on page 23, line 21 to page 25, line 19 provides exemplary PCR conditions for the primer pair of SEQ ID NOs: 15 and 16.

Moreover, one skilled in the art can readily determine conditions that are sufficient to amplify at least an internal portion of the argR gene as presently claimed. For example, the skilled artisan may perform PCR experiments while changing the annealing temperature, and then examining whether or not there is an argR gene in the PCR product. Applicants further note that several permutations of this technique and/or alternatives to the same are readily available through one of many treatises on PCR methodologies.

The Examiner is again reminded that the claimed invention provides, in part, a specific PCR scheme that is predicated on specific hybridization of both SEQ ID NOs: 15 and 16 to an appropriate template. This will not result in "any polynucleotide of any nucleotide sequence" as the Examiner has alleged, but rather would selectively amplify the argR gene of the bacterium used to provide the PCR template.

Applicants also wish to note that methods for disrupting a gene having a known sequence, or a gene having a similar sequence to the known sequence, are well known by the skilled artisan. For example, the artisan would readily appreciate that recombinant techniques

or a recombination event may be used to introduce a gene disruption. Therefore, disruption of a known gene function would require nothing beyond routine skill in the art.

In view of the foregoing, Applicants submit that with the specification in hand, coupled with the knowledge generally available in the art, the skilled artisan would readily appreciate how to make and use the invention as claimed. As such, Applicants note that the presently claimed invention meets the standard of enablement under 35 U.S.C. §112, first paragraph.

Therefore, withdrawal of this ground of rejection is requested.

Applicants submit that the present application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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LOCUS       AF041436                516 bp    DNA     linear   BCT 05-JAN-1
DEFINITION  Corynebacterium glutamicum arginine repressor (argR) gene, compl
            cds.
ACCESSION   AF041436
VERSION     AF041436.1
KEYWORDS    .
SOURCE      Corynebacterium glutamicum
  ORGANISM  Corynebacterium glutamicum
            Bacteria; Actinobacteria; Actinobacteridae; Actinomycetales;
            Corynebacterineae; Corynebacteriaceae; Corynebacterium.
REFERENCE   1  (bases 1 to 516)
  AUTHORS   Ko,S.-Y. and Lee,M.-S.
  TITLE     The argR gene of Corynebacterium glutamicum
  JOURNAL   Unpublished
REFERENCE   2  (bases 1 to 516)
  AUTHORS   Ko,S.-Y. and Lee,M.-S.
  TITLE     Direct Submission
  JOURNAL   Submitted (06-JAN-1998) Biology, Sookmyung Women's University,
            53-12 Chungpa-dong Yongsan-ku, Seoul 140-742, Korea
FEATURES             Location/Qualifiers
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                     ELGELLSGRTT"
BASE COUNT          118 a         154 c         136 g         108 t
ORIGIN
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       61  cgccaagctc tcattttgca gattttggac aaacaaaaag tcaccagcca ggtacaactg
      121  tctgaattgc tgctggatga aggcatcgat atcacccagg ccaccttgtc ccgagatctc
      181  gatgaactcg gtgcacgcaa ggttcgcccc gatgggggac gcgcctacta cgcggtcggc
      241  ccagtagata gcatcgcccg cgaagatctc cggggtccgt cggagaagct gcgccgcatg
      301  cttgatgaac tgctggtttc tacagatcat tccggcaaca tcgcgatgct gcgcaccccg
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      421  ggcaccatcg ctggtgatga caccgttttc gttctcgccc gtgatccgct cacaggtaaa
      481  gaactaggtg aattactcag cgggcgcacc acttaa
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